Measurements of Blood-Brain Barrier Integrity in Hippocampus of Patients with Mild Cognitive Impairment Using Dynamic Contrast-Enhanced MRI

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Purpose

The integrity of blood-brain barrier (BBB) may play a role in age-related deterioration and neurodegenerative diseases. Ultrastructural morphological and biochemical evidence have implicated the breakdown of BBB in Alzheimer's disease (AD), that probably precedes the neuronal damage and onset of dementia[1, 2, 3]. The defective BBB may allow circulating β-amyloid peptide (Aβ) to enter the brain, leading to a cascade of amyloid neurotoxic events. However, functional evidence with non-invasive imaging studies to support this finding is difficult to obtain. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has been widely used to evaluate brain tumors[4, 5]. In this study, we investigated whether DCE-MRI can be applied to detect subtle BBB leakage associated with pathological aging[6]. The enhancement kinetics measured from hippocampus and cerebellum in mild cognitive impairment (MCI) were compared to healthy controls. The derived vascular volume index and BBB permeability index were also correlated with subjects' cognitive performance scores.

Methods

Eleven MCI subjects (MCI, 7 men, 4 women; age: 73.9 ± 6.9 years) and 11 healthy age-matched elderly controls (controls, 5 men, 6 women; age: 74.4 ± 2.6 years) were studied. All subjects underwent a neuropsychological assessment and an MRI scan using a 1.5 Tesla Phillips Eclipse scanner. A T1-weighted gradient echo sequence with 16 acquisitions was prescribed to monitor the enhancement kinetics of Gd-DTPA-BMA (Omniscan®, 1 cc /10 lb body weight). The imaging parameters were TR = 10 ms, TE = 3 ms, flip angle = 20°, FOV = 22 cm, matrix size = 256 x 256, number of Averages = 1, Echo Train Length = 1. Twenty images with 8 mm slice thickness were acquired from the entire brain. Sixteen frames were prescribed for dynamic acquisition, and the temporal resolution for each frame was 25.5 s. The percent enhancement (post-contrast enhancement normalized to pre-contrast intensity) for each time point was obtained from ROIs outlined from the enhancing areas of bilateral hippocampus and cerebellum. The enhancement ratio at 30 sec after contrast injection was defined as the vascular volume index. At such an early time most contrast agents remain in the vessels, thus the enhancement is proportional to the vascular volume. The residual enhancement at 3-min post injection is associated with the amount of contrast agents leaked into the interstitial space, and this parameter normalized to the vascular volume was used as the BBB permeability index. In addition, the linear slope fitted from the peak to the end of the curve was obtained, which was used as another BBB permeability index. Slower decay indicates longer contrast retention thus a higher BBB leakage.

Results

Figure 1 shows the enhancement kinetics in MCI and controls. The right hippocampus of healthy controls had a higher magnitude ($p < 0.001$), also had a faster decay (tested using fitted slopes, $p < 0.05$) compared to MCI. The lower early enhancement in MCI suggested a lower vascular volume, and the slower decay in MCI indicated a longer signal retention possibly due to contrast leakage via compromised BBB. The enhancement magnitude measured from the left hippocampus was comparable between MCI and NC, but a slower decay rate was seen in the MCI. The enhancement curves measured from the cerebellum in these two groups were similar, with same early enhancement magnitude and decay. Table 1 summarizes the statistical analysis results. MCI subjects had a smaller vascular volume and a higher BBB permeability index in bilateral hippocampus than controls (*see* Table 1). The difference in the vascular volume index measured from right hippocampus was highly significant ($p = 0.001$). The vascular volume index measured from right hippocampus was significantly correlated with the score of Boston Naming Test (BNT, $r = 0.466$, $p = 0.04$), i.e. higher vascular volume associated with higher scores. There was a trend of negative correlation between BBB permeability index in right hippocampus and the score of BNT (i.e. higher BBB permeability associated with lower scores), although not statistically significant ($r = -0.404$, $p = 0.086$).

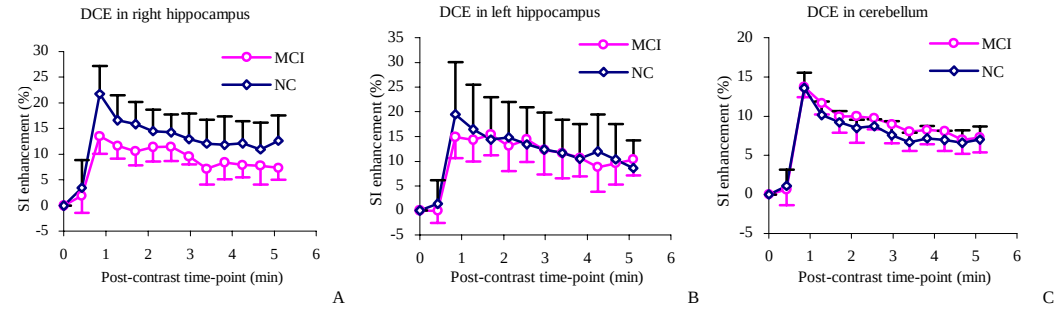

Fig 1. The % enhancement time course measured from right hippocampus (A), left hippocampus (B) and cerebellum (C). The right HP in MCI had a lower % enhancement. A slower decay rate was seen in R and L HP of MCI compared to NC.

Table 1. The vascular volume and blood-brain barrier (BBB) permeability index measured from bilateral hippocampus and cerebellum in MCI and healthy controls (mean ± SE).

	Vascular volume index			BBB permeability index		
	HP_R	HP_L	cerebellum	HP_R	HP_L	cerebellum
Controls (n=10)	**0.22 ± 0.02**	**0.20 ± 0.004**	**0.14 ± 0.007**	**0.58 ± 0.06**	**0.58 ± 0.04**	**0.51 ± 0.02**
MCI (n=11)	**0.14 ± 0.01***	**0.15 ± 0.01**	**0.14 ± 0.004**	**0.60 ± 0.06**	**0.72 ± 0.08**	**0.57 ± 0.04**

HP = hippocampus; R = right; L = left * $p = 0.001$, MCI vs. Controls

Discussion

In this study, we demonstrated that the DCE-MRI was applicable to investigate aging related vascular abnormality in human brain regions *in vivo*. The DCE curve obtained from the right hippocampus in MCI subjects showed a lower magnitude, indicating that the vascular volume was lower in MCI compared to controls. Since the ROI was drawn avoiding the atrophic region, the results indicated that the blood volume was lower in structurally intact tissues. Thus, one may argue that the right hippocampus may be at a higher risk of developing atrophy. A slower decay was seen in the enhancement kinetics of bilateral hippocampus in MCI compared to controls. This observation was probably related to leakage of contrast agent from capillaries into brain tissues via focal breached BBB. The result suggested that the integrity of cerebral microvasculature in hippocampus, particularly the right side, was compromised in MCI. The finding that vascular volume fraction was positively correlated with cognitive performance on BNT was encouraging, suggesting that the vascular characteristics of right hippocampus were, to some extent, associated with the certain cognitive function. In summary, we have demonstrated that DCE-MRI may provide a non-invasive means to measure the subtle BBB leakage associated with cerebrovascular pathology commonly found in AD, thus may provide an early indicator of pathological aging. It may also be helpful in predicting the disease progression from normal to MCI and also from MCI to AD.

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